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Early Life Antecedents of Atrial Fibrillation: Place of Birth and Atrial Fibrillation Related Mortality

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Abstract

Purpose—Recent evidence suggests early life factors correlate with atrial fibrillation (AF). We hypothesized that AF-related mortality, similar to stroke mortality, is elevated for individuals born in the southeastern US.

Methods—We estimated 3-year (1999-2001) average AF-related mortality rates, using US vital statistics for 55-89 year old whites (136,573 AF-related deaths) and blacks (8,288 AF-related deaths). We estimated age- and sex-adjusted odds of AF-related (contributing cause) mortality associated with birth state, and birth within the US stroke belt (SB), stratified by race. SB results were replicated using 1989-1991 data.

Results—Among blacks, four contiguous birth states were associated with statistically significant ORs>=1.25 compared to the national average AF-related mortality. The four highest-risk birth states for blacks also predicted elevated AF-related mortality among whites, but patterns were attenuated. The odds ratio for AF-related mortality associated with SB birth was 1.19 (CI 1.13, 1.25) for blacks and 1.09 (CI 1.07, 1.12) for whites, adjusting for SB adult residence.

Conclusion—Place of birth predicted AF-related mortality, after adjusting for place of adult residence. The association of AF related mortality and SB birth parallels that of other cardiovascular diseases, and may likewise indicate an importance of early life factors in the development of AF.

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Keywords

Atrial Fibrillation; Mortality; Residence; Geographic; Lifecourse

Introduction

Accumulated epidemiologic data link early life risk factors such as low birthweight and childhood socioeconomic status to a range of cardiovascular outcomes, including heart failure, myocardial infarction, stroke, and overall mortality.[1-6] However, little is known regarding the relationship between early environmental factors and the later development of arrhythmias. Recently, an association between higher birthweight and increased risk of AF has been reported, implicating a role for early life factors in the causal pathway for this most common, and morbid arrhythmia.[7]

The possible role of early life conditions in the etiology of AF is a challenge to study because there are few data sources; AF is transient and often asymptomatic, making assessment of the outcome difficult. Similarly, childhood social conditions are difficult to assess, which has led to the use of place of birth as a powerful proxy. Birthplace is a non-specific marker for a host of early life exposures and therefore especially valuable when little is known about specific risk factors. Birth in the southeastern United States is associated with elevated risk of stroke incidence and mortality.[8,9] Because of the strong association between AF and stroke[10], we hypothesized that AF and stroke exhibit similar geographic patterns, with elevations among people born in the “stroke belt” (SB; North Carolina, South Carolina, Georgia, Tennessee, Arkansas, Mississippi, or Alabama). Because AF is a well described independent risk factor for stroke[11], investigating whether geographic variation also exists in AF, and the relationship of these patterns to those of stroke may reveal clues to the underlying mechanism of these unexplained patterns. Environmental factors that influence cardiovascular pathology leading to stroke also may influence risk of developing AF, or AF may even play a mediating role for cerebrovascular disease in the SB.

To examine the possibility of geographic variation in the epidemiology of AF, we used national census and mortality data from 1989-1991 and 1999-2001 to assess the risk of AF-related mortality across the United States (US) by individual state of birth or state of adult residence and by residence in the SB. To rule out the possibility that geographic patterns were explained by differences in cause of death coding, we assessed whether geographic patterns of AF-related mortality persisted in out-migrants, who were born in the SB but lived elsewhere in adulthood.

Methods

Data sources

The 1990 and 2000 US Census Public Use Microsamples were examined to define the at-risk populations in 1990 and 2000, respectively.[12] These are 5% samples from the full census data, upweighted to represent the eligible US population in each year. Samples were restricted to individuals who were born in any of the 49 US states (excluding Hawaii) or the District of Columbia (DC), who resided in a US state or DC at ages 55-89 years on the census date, and who self-reported race as black or white. Mortality records for 1989-1991 and 1999-2001 were obtained from the National Center for Health Statistics cause of death files.[13] We pooled mortality records across three year periods to increase the stability of estimated mortality rates. The rates for 1990 were calculated using the deaths recorded in 1989-1991 (divided by three) as the numerator and the population at risk in the 1990 census as the denominator. The rates for 2000 were calculated using deaths recorded in 1999-2001

(divided by three) as the numerator and the population at risk in the 2000 census as the denominator. AF-related deaths were identified as those mortality records with contributing cause of death ICD-9 code 427.3 for 1990 and ICD-10 code I48 for 2000. In each analysis, mortality records and census data were used to calculate AF-related mortality rates for each combination of covariates and exposures: race, sex, and birth year and (depending on the analysis), state of birth, state of adult residence, SB birth, or SB adult residence.

It was determined by the Human Subjects Committee of the Harvard School of Public Health that the present research, consisting of secondary analyses of publicly available data sets did not constitute human subjects research.

Data collection and measurements

Exposures were defined based on state of birth or state of adult residence. Our definition of the SB comprised seven states (North Carolina, South Carolina, Georgia, Tennessee, Arkansas, Mississippi, or Alabama), corresponding to the US Department of Health & Human Services Stroke Belt Elimination Initiative and our own previous work.[14-16] We considered four SB exposure categories: born in the SB and residing in the SB during adulthood (individuals who were "doubly exposed"); the out-migrants, who were born in the SB but did not live there in adulthood (i.e., at census date); the in-migrants, who were born outside the SB but resided in the SB in adulthood; or neither born in the SB nor lived there in adulthood.

Analyses

Mortality rates were calculated by linking mortality and population data within each stratum defined by the exposure and covariates. We first used logistic regressions with random effects (SAS proc glimmix) for each state to estimate the odds of AF-related mortality for adult residents of each state (regardless of state of birth), adjusted for sex, age, and age-squared. We next repeated these models, estimating the odds of AF-related mortality for individuals who were born in each state (regardless of place of adult residence). Models were stratified by race. Empirical Bayes (shrinkage) estimates of the odds ratios (OR) associated with each state of adult residence and each state of birth were mapped. We used the Bayes estimates to account for uncertainty in estimates for states with small populations (this was especially relevant for estimating ORs among blacks by state of birth). This approach assumes that state-specific logistic regression coefficients are normally distributed around a national average; the shrinkage estimate pulls the predicted value for each state towards the national average, in inverse proportion to the variance of the effect estimate.[17,18] For states of birth that were identified as especially high or low-risk, we repeated the models restricting to migrants, i.e. those people whose state of birth differed from their state of residence in 2000. Due to sample size, this model could only be estimated for whites.

We examined whether there was an elevation in AF-related mortality specifically corresponding with birth or adult residence in the SB. We compared crude AF-related mortality rates for whites and blacks in four cross-classified SB exposure categories. We then used logistic regression (weighted to represent the eligible US population) to estimate race-stratified odds ratios for AF-related mortality for the following comparisons:

1. SB born vs. all others, adjusting for age and sex.
2. SB residence in adulthood vs. all others, adjusting for age and sex.
3. SB born vs. all others, adjusting for age, sex, and SB adult residence.
4. SB residence in adulthood vs. all others, adjusting for age, sex, and SB birth.

We next used logistic regression to estimate the age and sex-adjusted odds ratios for AF-related mortality in each of the four cross-classified SB exposure categories (SB doubly-exposed; SB out-migrants; SB in-migrants vs. those who did not live in the SB at birth or in adulthood). The cross-classified model allowed assessment of the independent or interactive effects of SB birth and adult residence. We also examined models stratified by sex and age (55-64, 65+). We interpreted a lack of overlap of 95% confidence intervals (CI) as evidence that the two coefficients were significantly different (a highly conservative approach[19,20]). We estimated the fraction of AF-related mortality among individuals born in the SB that would have been prevented if the SB born had the same AF-related mortality rates as individuals born outside the SB using the formula: (OR-1)/OR.[21]

In all models, we show race-stratified results, adjusting for sex and age modelled using both linear and quadratic terms. Analyses were conducted using SAS 9.2 software for windows (SAS Institute Incorporated, Cary, NC, USA).

Results

The at-risk population in 1990 included 41.5 million whites (56% women, average age 68 years) and 4.2 million blacks (59% women, average age 67 years); in 2000, the at risk population included 45.2 million whites (55% women, average age 68 years) and 4.7 million blacks (59% women, average age 67 years). (Table 1).

Whites born in Maryland, West Virginia, or North Carolina had a statistically significant higher risk for AF-related mortality (OR > 1.25) compared to the national average of this racial group. (Figure 1a). Conversely, whites born in Louisiana had nearly 35% lower odds of AF-related mortality compared to the national average (OR=0.66; 0.61, 0.70). When analyses were repeated restricting to migrants who did not live in the same state at birth and in 2000, the odds ratios were elevated among people born in West Virginia (OR=1.25; 1.17, 1.33) and North Carolina (OR=1.10; 1.02, 1.18) but not Maryland (OR=0.97; 0.90, 1.06) (results not shown). In the migrant-models, individuals born in Louisiana experienced lower odds of AF-related mortality (OR=0.85) than the national average.

Geographic patterning also was evident among blacks (Figure 1b). Blacks born in North Carolina, Maryland, South Carolina, and Virginia had a statistically significant higher risk for AF-related mortality (OR > 1.25) compared to the national average for this racial group. Blacks born in Michigan, New York, or Iowa experienced at least 25% lower odds of AF-related mortality than the national average.

AF-related mortality was elevated in several classic SB states, such as the Carolinas, but not in others, such as Mississippi. We contrasted AF-related mortality rates in SB states versus all other states. Table 1 presents the population estimates and crude AF-related mortality rates. The highest crude rates of AF-related mortality were observed among those who were neither born in the SB nor resided there in adulthood. Crude AF-related mortality rates were lower for blacks in each of the exposure categories. Because of substantial differences in age- and sex- adjusted patterns for each of the SB exposure groups, we next conducted analyses adjusting for age and sex. After adjustment, whites born in the SB (Table 2, left panels) had a non-significant 2% elevation in odds of AF-related mortality (95% CI: 1.00, 1.05) in 1990, compared to whites born outside the SB. In 2000, whites born in the SB had a 9% (95% CI: 1.07, 1.10) elevation in odds of AF-related mortality. SB adult residence was associated with even smaller ORs among whites, in both 1990 and 2000. When simultaneously adjusting for SB birth and SB adult residence (Table 2, right panels), SB birth was associated with AF related mortality in 1990 (OR=1.05; 95% CI: 1.02, 1.09) and 2000 (OR=1.09; 95% CI: 1.07, 1.12). In contrast, after adjustment for SB birth, adult SB

residence was not associated with AF-related mortality among whites in either 1990 or 2000.

For blacks, SB birth was associated with 21% higher odds of AF-related mortality (95% CI: 1.14, 1.28) in 1990 and 19% higher odds of AF-related mortality (95% CI: 1.14, 1.24) in 2000. Without adjustment for SB birth, SB adult residence among blacks was associated with 9% higher odds of AF-related mortality in 1990 (95% CI: 1.02, 1.16) and 10% higher odds in 2000 (95% CI: 1.05, 1.15). When SB birth and SB adult residence were both included in the model, only SB birth remained significantly associated with AF-related mortality. Adjusted for SB adult residence, blacks born in the SB experienced 22% and 19% higher odds of AF-related mortality in 1990 and 2000, respectively, compared to blacks born elsewhere.

When considering the four exposure categories simultaneously (Table 3), SB birth was associated with small elevations in AF-related mortality for whites who either lived in the SB in adulthood (OR=1.08) or lived outside the SB in adulthood (OR=1.06), compared to those who were born outside the SB and also lived outside the SB in adulthood. Among blacks, SB birth also was associated with moderate elevations in AF-related mortality among individuals who remained in the SB in adulthood (OR=1.18) or lived outside the SB in adulthood (OR=1.20). For both the doubly-exposed and the SB out-migrants, the OR for blacks was significantly higher than the OR for whites, as indicated by non-overlapping 95% CIs.

Because the high risk geographic region shown in the maps did not correspond well with the SB, we conducted post-hoc analyses defining the AF risk zone as a contiguous region including the District of Columbia, Maryland, North Carolina, South Carolina, Virginia, and West Virginia. Whites born in this zone had an OR of 1.31 (95 % CI: 1.29, 1.33) for AFRM compared to whites born in the rest of the country. Blacks born in this zone had an OR of 1.43 (95% CI: 1.37, 1.50).

Discussion

We found a statistically significant elevation in odds of AF-related mortality associated with state of birth. The four highest-risk states were geographically contiguous, suggesting that the association is unlikely to be due to chance. Some high-risk states were part of the SB, and we found modest elevations in odds of AF-related mortality associated with birth in the SB, especially for blacks. Adult residence in the SB was not associated with AF-related mortality after adjustment for birth in the SB, suggesting that the elevations were unlikely to be explained by differences in diagnosis rates or cause-of-death coding patterns. Strikingly, however, some states traditionally considered part of the SB, such as Mississippi and, for whites, Arkansas, were associated with lower than national average rates of AF-related mortality.

The current analyses have several strengths and limitations. The study presents data by place of birth for the entire US, which is available in very few cohort studies. States are large and heterogeneous geographic units, but are the lowest level of geographic detail for birthplace available in both the census and death certificate data. We may have misclassified variation that might be apparent at a more detailed geographic level.(19) We only know state of residence at two points in the lifecourse: birth and death, which may misrepresent exposures for people who migrated soon after birth or shortly before death. However, most people remain in their state of birth at least through adolescence, and nearly everyone living in the SB in 2000 had lived there for at least 5 years.[12,22] AF is associated with numerous clinical

risk factors, and we were not able to adjust our findings for these important covariates, which include obesity, hypertension, diabetes, and structural heart disease.

Differential geographic and racial patterns in AF diagnoses and cause of death coding on mortality records may introduce bias in these results.[23] Death certificate coding has imperfect sensitivity and specificity, [24] but such limitations seem unlikely to account for patterns of AF-related mortality by place of birth. Coding for cause of death may differ regionally, but we anticipate this would be most influenced by place of death, not birth place. Therefore, it is difficult to attribute geographic patterns by place of birth that are evident among inter-state migrants to death certificate coding.[25,26]

Our findings are consistent with a large body of prior work demonstrating the importance of early life factors in the development of cardiovascular diseases such as stroke and coronary artery disease. [1-6,27,28] There are many possible mechanisms linking adversity in childhood and adult cardiovascular disease (Figure 2), including nutritional deprivation altering the trajectory of organ and vasculature development; psychosocial stressors inducing long term alterations in stress response, inflammation, and infectious exposures, leading to accumulation of allostatic load throughout life; and the formation of life-long behavioral patterns regarding smoking, diet, adiposity or exercise.[29,30] Many of these mechanisms are probably geographically patterned.[31-35] The relative importance of these alternative mechanisms is not well established, and this is a priority area in lifecourse epidemiology.

Our study is among the first to address early life etiologies for AF. The only prior study relating birthweight to AF found patterns that were in the opposite direction as those for other cardiovascular outcomes, suggesting unique pathways of early life influence on AF.[7] Since little is currently known about behavioral, social, or environmental risk factors for AF, identifying the specific factors mediating the association between AF-related mortality and place of birth may help elucidate the etiology of AF.

Multiple studies have demonstrated that despite a higher burden of AF risk factors, blacks have a paradoxically lower incidence and prevalence of AF than their white counterparts; a recent report indicates this finding may be due to underlying genetic variation.[36-39] This result has led to speculation about possible distinct aspects of the etiology of AF among blacks. Our results showed that among whites, SB-birth was associated with only small and inconsistent elevations in AF-related mortality. Among blacks, SB-birth predicted 18-23% higher odds of AF-related mortality (depending on the model). The reason that SB birth is more strongly related with AF-related mortality risk among blacks than whites is uncertain, but may be attributable to the extreme socioeconomic and psychosocial adversity encountered by blacks in the South, or by genetic variation.[40-42]

Birthplace is associated with AF-related mortality, accounting for age, sex, and place of adult residence. These findings are consistent with a role for early life factors in the course of AF, the most common arrhythmia. Further research in lifecourse risk factors may reveal hitherto unknown therapeutic targets for prevention.

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List of Abbreviations

AF	atrial fibrillation
CI	confidence interval
OR	odds ratio
SB	stroke belt
US	United States

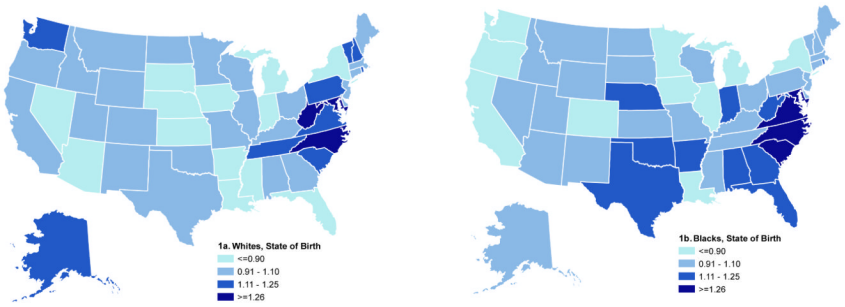

Figure 1. Odds ratio for AF-related mortality for state of birth, compared to the national average, based on empirical Bayes (shrinkage) random effect estimates from logistic models

(1a) Odds ratio for AF-related mortality for whites by state of birth, (1b) Odds ratio for AF-related mortality for blacks by state of birth.

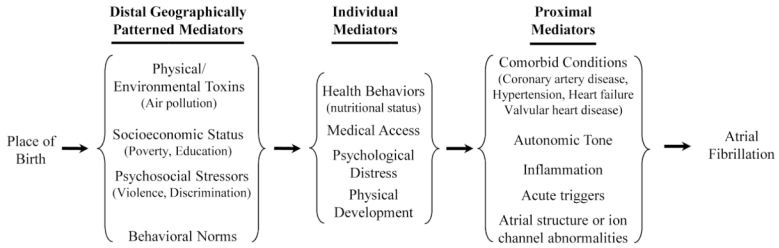

Figure 2. Possible mechanisms linking place of birth and risk of atrial fibrillation

Table 1

Crude AF-related mortality rates by race, Stroke Belt birth, and Stroke Belt adult residence, 1990 and 2000

Born in Stroke Belt	Yes						No					
Resided in Stroke Belt at Death	Yes			No			Yes			No		
	Fatalities (1999-2001)	Population (1,000s)	Annual Rate per 100,000*	Fatalities (1999-2001)	Population (1,000s)	Annual Rate per 100,000*	Fatalities (1999-2001)	Population (1,000s)	Annual Rate per 100,000*	Fatalities (1999-2001)	Population (1,000s)	Annual Rate per 100,000*
Full Sample												
1990	7,411	5,028	49	3,535	2,575	46	1,170	997	39	55,474	37,081	50
2000	15,614	5,504	95	6,839	2,673	85	3,347	1,510	74	119,061	40,176	99
Whites												
1990	6,067	3,972	51	2,134	1,380	52	1,131	956	39	53,741	35,176	51
2000	13,268	4,348	102	4,440	1,428	104	3,257	1,435	76	115,608	37,965	102
Blacks												
1990	1,344	1,057	42	1,401	1,194	39	39	41	32	1,733	1,905	30
2000	2,346	1,155	68	2,399	1,246	64	90	75	40	3,453	2,210	52

Restricted to black and white US residents ages 55-89 born in the United States (excluding Hawaii). Fatalities include any death with atrial fibrillation (1990) or atrial fibrillation or flutter (2000) listed as a contributing cause.

Fatalities are based on data pooled from 1989, 1990, and 1991 (for 1990 average) or 1999, 2000, and 2001 (for 2000 average)

Annual rate is calculated as the 3-year total fatalities divided by the 3 times the 1990 or 2000 Census population.

Table 2

Age and sex adjusted odds ratios for AF-related mortality

	Birth and Adult Residence Modeled Separately				Birth and Adult Residence Modeled Together			
	Born In the Stroke Belt vs Born Outside the Stroke Belt		Adult Residence In the Stroke Belt vs Adult Residence Outside the Stroke Belt		Adult Residence In the Stroke Belt vs Adult Residence Outside the Stroke Belt*		Born In the Stroke Belt vs Born Outside the Stroke Belt†	
Full Sample	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
1990 (n=45,681‡)	1.04	(1.02, 1.07)	1.01	(0.98, 1.03)	0.95	(0.92, 0.98)	1.08	(1.05, 1.12)
2000 (n=49,863‡)	1.10	(1.08, 1.11)	1.06	(1.04, 1.08)	0.98	(0.96, 1.01)	1.11	(1.09, 1.13)
Whites								
1990 (n=41,484‡)	1.02	(1.00, 1.05)	1.00	(0.98, 1.03)	0.96	(0.93, 1.00)	1.05	(1.02, 1.09)
2000 (n=45,177‡)	1.09	(1.07, 1.10)	1.06	(1.04, 1.08)	0.99	(0.97, 1.02)	1.09	(1.07, 1.12)
Blacks								
1990 (n=4,197‡)	1.21	(1.14, 1.28)	1.09	(1.02, 1.16)	0.97	(0.91, 1.05)	1.22	(1.14, 1.31)
2000 (n=4,686‡)	1.19	(1.14, 1.24)	1.10	(1.05, 1.15)	0.99	(0.94, 1.05)	1.19	(1.13, 1.25)

Restricted to US residents ages 55-89 born in the United States (excluding Hawaii).

All models adjusted for sex, age and age squared, and “full sample” models additionally adjusted for race.

*Additionally adjusted for stroke belt birth

†Additionally adjusted for stroke belt adult residence

‡Weighted n for the at risk population.

Table 3

Odds ratios for AF-related mortality associated with Stroke Belt birth and Stroke Belt adult residence in subgroups stratified by race, 1990 and 2000

	Stroke Belt Birth; Stroke Belt Adulthood		Non-Stroke Belt Birth; Stroke Belt Adulthood		Stroke Belt Birth; Non-Stroke-Belt Adulthood	
	OR	95% CI	OR	95% CI	OR	95% CI
White[*]						
1990	1.02	(0.99, 1.04)	0.93	(0.88, 0.99)	1.04	(0.99, 1.08)
2000	1.09	(1.07, 1.11)	0.96	(0.92, 0.99)	1.07	(1.04, 1.10)
Black[*]						
1990	1.19	(1.11, 1.28)	1.03	(0.75, 1.42)	1.23	(1.14, 1.32)
2000	1.18	(1.12, 1.25)	0.90	(0.73, 1.11)	1.18	(1.12, 1.25)

Parameter estimates are compared to the reference group of people who were neither born in the Stroke Belt nor resided in the Stroke Belt in adulthood. All models are adjusted for age and age^2.

[*]Additionally adjusted for sex.